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Therapeutic Class Review
Non-Benzodiazepine, Non-Barbiturate Sedative Hypnotics

I. Overview

Primary insomnia is poor-quality sleep or difficulty in initiating or maintaining sleep that lasts for at least one month, causing marked distress or impairment in occupational, social, or other important areas of functioning.[1] In primary insomnia, the sleep disturbance is not due to another sleep disorder (eg, narcolepsy), mental illness, medication(s), drug of abuse, or general medical condition.[1] Insomnia may be further classified as transient insomnia (1-3 nights), short-term insomnia (3 nights to 1 month), and chronic insomnia ($\geq$1 month), based upon the duration of symptoms.[2] In the United States (US), at least one-third of adults are estimated to have experienced intermittent symptoms of insomnia, with at least 10% experiencing chronic insomnia.[2] Management of insomnia is most effective when the choice of treatment is patient specific, taking into consideration the patient's age, duration and severity of symptoms, and etiology of insomnia if known.[3] All pharmacotherapy should be used with appropriate caution, at minimum effective doses and for a minimum duration of time.[2] Nonpharmacologic strategies have been shown to be effective in the treatment of insomnia, and for some patients may be more effective than drugs for the treatment of chronic insomnia.[2,4,5]

Traditional benzodiazepines exhibit their sedative-hypnotic properties through a nonselective binding to the receptors on the gamma-aminobutyric acid$_A$ ($GABA_A$) receptor complex.[2,3,6-8] As a result, these drugs have both desirable therapeutic properties (eg, anxiolytic, sedative, anticonvulsant, and muscle-relaxant properties) and undesirable effects (eg, central nervous system depression, cognitive and psychomotor impairment, residual daytime sedation, tolerance and withdrawal). Newer, non-benzodiazepine, non-barbiturate sedative hypnotics (eg, eszopiclone, zaleplon, and zolpidem) are more selective when binding to the $GABA_A$ complex.[6] Ramelteon, on the other hand, has no affinity for the $GABA_A$ receptor complex. Ramelteon is a melatonin receptor, full-agonist that is more selective for the melatonin type 1 (MT_1) and type 2 (MT_2) receptors compared to the type 3 (MT_3) receptor in the suprachiasmatic nucleus of the hypothalamus. The MT_1 and MT_2 receptors are thought to be involved in the maintenance of the circadian rhythm underlying the normal sleep-wake cycle. Tolerance, rebound insomnia or withdrawal effects have not been observed with ramelteon, and ramelteon is not a controlled substance.[5]

The non-benzodiazepine, non-barbiturate sedative hypnotics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Chloral hydrate, zolpidem, and zoleplon are available in at least one generic dosage form.

Table 1. Non-Benzodiazepine, Non-Barbiturate Sedative Hypnotics Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)
chloral hydrate	capsule, rectal suppository, syrup	Somnote®
eszopiclone	tablet	Lunesta®
ramelteon	tablet	Rozerem®
zaleplon	capsule	Sonata®*
zolpidem	extended-release tablet, tablet	Ambien®*, Ambien® CR

*Generic is available in at least one dosage form or strength.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the non-benzodiazepine, non-barbiturate sedative hypnotics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Non-Benzodiazepine, Non-Barbiturate Sedative Hypnotics

Clinical Guideline	Recommendation(s)
American Academy of Sleep Medicine (AASM), Standards of Practice Committee: **Practice Parameters for the Psychological and Behavioral Treatment of Insomnia: An Update (2006)**[4]	• Insomnia as a primary disorder is known as "primary insomnia," as opposed to insomnia due to or associated with another condition such as medical or psychiatric illness, substance abuse disorder, or another sleep disorder. The latter is referred to in the guideline as "secondary insomnia." • Psychological and behavioral interventions are effective and recommended in the treatment of both chronic primary insomnia and secondary insomnia. • Stimulus control is effective in the treatment of chronic insomnia and involves training that reassociates the bed and bedroom with sleep and promotes a consistent sleep-wake schedule. • Chronic insomnia is effectively treated with relaxation training (progressive muscle relaxation) and autogenic training to reduce tension, as well as reduce disruptive thoughts at bedtime. • Sleep restrictions, such as limiting time in bed to actual time asleep, are useful in chronic insomnia. • Cognitive behavior therapy, with or without relaxation therapy, is recommended in the treatment of chronic insomnia. This form of therapy focuses on changing patient beliefs and attitudes about insomnia. Stimulus control therapy, sleep restriction, relaxation training and sleep hygiene education may also be involved. • Paradoxical intention, where the patient attempts to stay awake, is effective in sleep initiation insomnia. • The use of visual or auditory biofeedback to reduce somatic arousal is useful in chronic insomnia. • There is insufficient evidence that sleep hygiene monotherapy is effective. • Imagery training has not been proven effective as monotherapy or in combination with other approaches. • There is limited evidence that cognitive therapy alone is effective in treating insomnia. • Insufficient evidence was available to recommend one single therapy over another, or to recommend single therapy versus a combination of psychological and behavioral interventions. • Psychological and behavioral interventions are effective and recommended in treating insomnia in older adults. • Psychological and behavioral interventions are effective in treating insomnia in chronic hypnotic users.
National Institutes of Health (NIH), State-of-the-Science Conference Statement: **Manifestations and Management of Chronic Insomnia in Adults (2005)**[9]	Conference Statement • "Evidence supports the efficacy of cognitive-behavioral therapy and benzodiazepine receptor agonists in the treatment of this disorder [chronic insomnia], at least in the short term. Very little evidence supports the efficacy of other treatments, despite their widespread use." General Considerations • The most common treatments used by individuals with chronic insomnia are prescription medications, over-the-counter antihistamines, and alcohol. • The major forms of psychological treatments are cognitive and behavioral therapies. Prescription Medications with Food and Drug Administration (FDA) Approval for the Treatment of Insomnia • Benzodiazepine receptor agonists include benzodiazepines (eg, flurazepam, temazepam, and triazolam) as well as nonbenzodiazepine-structured anxiolytic agents acting at benzodiazepine receptors (eg, eszopiclone, zaleplon, and zolpidem). • Benzodiazepine receptor agonists have been shown to be effective in the short-term management of insomnia.

Clinical Guideline	Recommendation(s)
	• The frequency and severity of the adverse effects are much lower for the newer benzodiazepine receptor agonists, most likely because these agents have shorter half-lives. • In the short term, abuse of the benzodiazepine receptor agonists is not a major problem, but problems associated with their long-term use require further study. • Barbiturates (eg, phenobarbital) have been used in the treatment of insomnia; however, short-term and long-term studies are lacking; such drugs bear significant risks and are not recommended in the treatment of chronic insomnia. • Antidepressants (especially trazodone) are often prescribed for insomnia although they are not FDA approved for this purpose. In short-term use, trazodone and doxepin have been shown to have some beneficial effects, but there are no studies on long-term use. Data on other antidepressants (eg, amitriptyline and mirtazapine) in individuals with chronic insomnia are lacking. • These guidelines were published prior to the FDA approval of ramelteon. <u>Nonprescription Medications</u> • Antihistamines (eg, diphenhydramine) are the most commonly used over-the-counter agents for chronic insomnia; however, there is no systematic evidence for efficacy and there are significant concerns about the risks of these medications. <u>Behavioral and Cognitive Therapies</u> • Behavioral methods include relaxation training, stimulus control, and sleep restriction. • Cognitive therapy methods have been added to behavioral methods and include cognitive restructuring, in which anxiety-producing beliefs and erroneous beliefs about sleep and sleep loss are specifically targeted. • The combination of cognitive methods and behavioral methods (CBT) has been found to be as effective as prescription medications for short-term treatment of chronic insomnia. The beneficial effects of CBT may last well beyond the termination of active treatment.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Treatment of Insomnia (2006)**[5]	• Short-term use of a short-acting nonbenzodiazepine benzodiazepine receptor agonist (NBRA) is generally effective and safe (minimal adverse events and drug interactions), but it is not clear that NBRAs are more effective or safer than benzodiazepines. • Short-acting benzodiazepines and NBRAs may not prevent early morning awakening; when this occurs, a drug with an intermediate duration of action may be more helpful. • Nonprescription first generation antihistamines such as diphenhydramine are not recommended for treatment of insomnia; tolerance develops quickly and they can cause next-day sedation that impairs driving skills. • Cognitive behavioral therapy is safer and in some patients may be more effective than drugs for the treatment of chronic insomnia. • Barbiturates and chloral hydrate are not recommended due to their many side effects and the possibility of physical dependence and abuse.

III. Indications

Food and Drug Administration (FDA)-approved indications for the non-benzodiazepine, non-barbiturate sedative hypnotics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Non-Benzodiazepine, Non-Barbiturate Sedative Hypnotics [6-8,10-15]

Drug	Alcohol Withdrawal Syndrome	Anxiety Due to Drug Withdrawal	Insomnia	Insomnia, Short-Term	Sedation
Chloral hydrate	✔	✔ (eg, narcotics, barbiturates)		✔	✔ (routine, preoperative, prior to electro-encephalographic evaluation)
Eszopiclone			✔ * (decreased sleep latency and improved sleep maintenance)		
Ramelteon			✔ † (characterized by difficulty with sleep onset)		
Zaleplon				✔ ‡ (decreased time to sleep onset)	✔ (routine or preoperative)
Zolpidem immediate-release				✔ § (characterized by difficulty with sleep initiation)	
Zolpidem, extended-release			✔ ‖ (characterized by difficulties with sleep onset and/or sleep maintenance)		

* The clinical trials performed in support of efficacy were up to 6 months in duration. Studies were conducted in patients with transient and chronic insomnia.
† The clinical trials reported in the product labeling were conducted in patients with transient and chronic insomnia and lasted up to 35 days in duration.
‡ The clinical trials performed in support of efficacy ranged from single night to 5 weeks in duration. Studies were conducted in patients with transient and chronic insomnia.
§ The clinical trials performed in support of efficacy were 4-5 weeks in duration and conducted in patients with transient and chronic insomnia.
‖ The clinical trials performed in support of efficacy were up to 3 weeks (using polysomnography measurement up to 2 weeks in both adult and elderly patients) and 24 weeks (using patient reported assessment in adult patients only) in duration. The studies were conducted in patients with chronic primary insomnia.

IV. Pharmacokinetics

The pharmacokinetic parameters for the non-benzodiazepine, non-barbiturate sedative hypnotics are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Non-Benzodiazepine, Non-Barbiturate Sedative Hypnotics[2,6-8,10-15]

Drug	Bioavailability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Chloral hydrate	Well absorbed orally and rectally	70-80	Hepatic	Yes; trichloroethanol	Biliary (N/A), renal (N/A)	8-11
Eszopiclone	80%	52-59	Hepatic (CYP3A4 and CYP 2E1)	Yes; (S)-N-desmethylzopiclone	Not reported	6
Ramelteon	Total absorption is at least 84%; however, absolute oral bioavailability is 1.8%	82	Hepatic (CYP1A2)	Yes; M-II	Fecal (4), renal (84)	1-2.6
Zaleplon	30	60	Hepatic (aldehyde oxidase and CYP3A4)	None	Fecal (17), renal (71)	1
Zolpidem	70	93	Hepatic (mainly CYP3A4, also CYP1A1 and CYP2D6)	None	Biliary (N/A), fecal (N/A), renal (N/A)	2.5 (immediate-release) 2.8 (controlled-release)

N/A=not available

V. Drug Interactions

Significant drug interactions with the non-benzodiazepine, non-barbiturate sedative hypnotics are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with the Non-Benzodiazepine, Non-Barbiturate Sedative Hypnotics [7,8]

Drug(s)	Significance Level	Interaction	Mechanism
Ramelteon	1	Fluvoxamine	Fluvoxamine is a strong inhibitor of CYP1A2, the main metabolizing enzyme for ramelteon. Ramelteon should not be used in combination with fluvoxamine.
Chloral hydrate	2	Ethanol	Concurrent ingestion of chloral hydrate and ethanol synergistically increases central nervous system (CNS) depression. Disulfiram-like reactions, while rare, have been reported when alcohol is consumed after chloral hydrate.
Eszopiclone	2	Ketoconazole	Concomitant use of eszopiclone and ketoconazole may result in increased plasma concentrations of eszopiclone due to the CYP3A4-mediated inhibition of eszopiclone metabolism by

Drug(s)	Significance Level	Interaction	Mechanism
			ketoconazole. Increased eszopiclone plasma concentrations may result in increased side effects.
Ramelteon	2	Fluconazole, ketoconazole	Fluconazole and ketoconazole inhibit CYP2C9 and CYP3A4, respectively, resulting in increased exposure to ramelteon and increased risk of side effects.
Zaleplon	2	Cimetidine	Cimetidine may inhibit the metabolism (aldehyde oxidase and CYP3A4) of zaleplon resulting in a potentiation of zaleplon effects.
Zaleplon	2	Rifampin	Rifampin may induce the CYP3A4 metabolism of zaleplon resulting in a reduction in efficacy for zaleplon.
Zolpidem	2	Azole antifungals (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	Azole antifungal agents may interfere with the major route of zolpidem metabolism (CYP3A4). Plasma concentrations and therapeutic effects of zolpidem may be increased. The effects on zolpidem appear to be greatest with ketoconazole.
Zolpidem	2	Bupropion, desipramine, fluoxetine, sertraline, venlafaxine	Hallucinations after concurrent use of zolpidem and antidepressant medication have been reported. The hallucination episodes all lasted longer than one hour, but resolved without further sequelae.
Zolpidem	2	Rifampin	Rifampin may increase the metabolism of zolpidem resulting in decreased plasma levels and pharmacodynamic effects of zolpidem.
Zolpidem	2	Ritonavir	Ritonavir may inhibit the hepatic metabolism of zolpidem leading to possibly severe sedation and respiratory depression. Concurrent administration of zolpidem and ritonavir is contraindicated.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the non-benzodiazepine, non-barbiturate sedative hypnotics are noted in Table 6. A black box warning regarding chloral hydrate is noted in Table 7.

In March of 2007 the FDA issued a press release regarding its request that all drug manufacturers of medications approved for the treatment of sleep disorders revise product labeling to include warnings and potential risks of adverse events. Various products containing eszopiclone, ramelteon, zaleplon, and zolpidem were among the drugs targeted in the alert. These adverse events include severe allergic reaction and angioedema, as well as complex sleep-related behaviors including sleep-driving, making phone calls and eating and preparing food while asleep. The FDA has also requested that consumers be informed through the development of a Patient Medication Guide.[16]

Table 6. Common Adverse Events (%) Reported with the Non-Benzodiazepine, Non-Barbiturate Sedative Hypnotics [6-8,10-15]

Adverse Event	Chloral Hydrate	Eszopiclone	Ramelteon	Zaleplon	Zolpidem IR	Zolpidem ER
Cardiovascular						
Cerebrovascular disorder	-	-	-	-	≤1	≤1
Chest pain	-	≥1	-	≥1	1	≤1
ECG changes, transient	-	-	-	-	-	-
Hypertension	-	-	-	-	≤1	≤1

Adverse Event	Chloral Hydrate	Eszopiclone	Ramelteon	Zaleplon	Zolpidem IR	Zolpidem ER
Hypotension (includes postural)	-	-	-	-	≤1	≤1
Migraine	-	≥1	-	≥1	≤1	≤1
Palpitation	-	-	-	-	2	2
Peripheral edema	-	≥1	-	≤1	-	≤1
Syncope	-	-	-	-	≤1	≤1
Tachycardia	-	-	-	-	≤1	≤1
Central Nervous System						
Agitation	-	-	-	-	≤1	≤1
Amnesia/ memory disorder	-	-	-	2-4	1	1-3
Anxiety	-	1-3	-	≥1	1	2-3
Ataxia	✔	-	-	-	>1	1
Confusion	✔	≤3	-	≤1	>1	3
Convulsions	-	-	-	-	-	-
Decreased concentration	-	-	-	≥1	≤1	2
Depersonalization	-	-	-	≤2	≤1	1
Depression	-	1-4	2	≥1	2	1-2
Disinhibition	-	-	-	-	-	1
Dizziness	✔	1-7	5	7-9	1-5	8-12
Dream disturbances	-	1-3	-	-	1	≤1
Drowsiness	-	-	-	-	2-8	>1
Emotional lability	-	-	-	-	≤1	1
Euphoria	-	-	-	-	>1	1
Excitement	✔	-	-	-	-	-
Falling	-	-	-	-	≤1	≤1
Fatigue	-	-	4	-	1	3
Hallucinations	✔	1-3	-	≤1	≤1	4
Headache	-	13-21	7	30-42	7-19	14-19
Hypesthesia	-	-	-	≤2	-	-
Hypertonia	-	-	-	1	-	-
Hypoesthesia	-	-	-	-	≤1	2
Illusion	-	-	-	-	≤1	≤1
Incoordination	✔	-	-	-	-	2
Insomnia	-	-	3	-	>1	>1
Lethargy	-	-	-	-	3	>1
Libido decreased	-	≤3	-	-	-	-
Lightheadedness	✔	-	-	-	2	>1
Malaise	-	-	-	≤2	≤1	≤1
Nervousness	-	≤5	-	≥1	1	≤1
Neuralgia	-	≤3	-	-	-	-
Numbness/ paresthesia	-	-	-	3	≤1	≤1
Psychomotor retardation	-	-	-	-	-	2
Sedation, residual	✔	-	-	-	3	>1
Sleep disorder	-	-	-	-	1	≤1
Somnolence	✔	8-10	5	5-6	3	6-15
Speech disorder	-	-	-	-	≤1	≤1
Stupor	-	-	-	-	≤1	≤1
Tremor	-	-	-	2	≤1	1
Vertigo	-	-	-	≤1	>1	2
Dermatological						
Angioedema	✔	-	-	-	✔	✔
Bullous lesions	✔	-	-	-	-	-

Adverse Event	Chloral Hydrate	Eszopiclone	Ramelteon	Zaleplon	Zolpidem IR	Zolpidem ER
Eczema	✔	-	-	-	-	-
Edema	-	-	-	-	≤1	≤1
Erythema multiforme	✔	-	-	-	-	-
Pallor	-	-	-	-	≤1	≤1
Photosensitivity reaction	-	-	-	≤1	-	-
Pruritis	-	1-4	-	≥1	≤1	≤1
Purpura	✔	-	-	-	-	-
Rash	✔	3-4	-	≥1	2	1
Skin wrinkling	-	-	-	-	-	1
Urticaria	✔	-	-	-	-	1
Endocrine and Metabolic						
Blood cortisol decreased	-	-	1	-	-	-
Hyperglycemia	-	-	-	-	≤1	≤1
Hyperkalemia	-	-	-	-	-	-
Gastrointestinal						
Abdominal pain	✔	✔	-	6	2	>1
Anorexia/ weight loss	-	-	-	≤2	1	≤1
Appetite disorder	-	-	-	-	-	1
Colitis	-	-	-	≤1	-	-
Constipation	-	-	-	≥1	2	2
Diarrhea	✔	2-4	2	-	1-3	>1
Dry mouth	-	3-7	-	≥1	3	>1
Dyspepsia	-	2-6	-	≥1	5	>1
Dysphagia	-	-	-	-	≤1	≤1
Flatulence	-	-	-	-	≤1	1
Gastroenteritis	-	-	-	-	≤1	1
Hiccup	-	-	-	-	>1	>1
Nausea	✔	4-5	3	6-8	2-6	7
Thirst	-	-	-	-	≤1	≤1
Vomiting	✔	≤3	-	-	1	1
Laboratory Test Abnormalities						
Abnormal hepatic function	-	-	-	-	≤1	≤1
SGPT elevation	-	-	-	-	≤1	≤1
Musculoskeletal						
Arthralgia	-	-	2	≥1	4	>1
Arthritis	-	-	-	≥1	≤1	≤1
Back pain	-	✔	-	≥1	3	4
Leg/muscle cramps	-	-	-	-	≤1	2
Myalgia	-	✔	2	≥1	1-7	4
Neck pain	-	-	-	-	-	1-2
Weakness	-	✔	-	5-7	>1	>1
Respiratory						
Bronchitis	-	-	-	≥1	≤1	≤1
Coughing	-	-	-	-	≤1	≤1
Dyspnea	-	-	-	-	≤1	≤1
Epistaxis	-	-	-	≤1	-	-
Lower respiratory tract infection	-	-	-	-	-	1
Pharyngitis	-	✔	-	-	3	6
Pleural effusion	-	-	-	-	-	-
Rhinitis	-	✔	-	-	1	≤1
Sinusitis	-	-	-	-	4	>1

Adverse Event	Chloral Hydrate	Eszopiclone	Ramelteon	Zaleplon	Zolpidem IR	Zolpidem ER
Throat sore/ irritation	-	-	-	-	-	1
Upper respiratory tract infection	-	5-10	3	-	5	>1
Special Senses						
Conjunctivitis	-	-	-	≥1	-	-
Dysgeusia/ taste perversion	-	8-34	2	≥1	≤1	≤1
Ear pain	-	-	-	≤1	-	-
Eye pain	-	-	-	3-4	≤1	≤1
Eye redness/itching	-	-	-	-	≤1	2
Hyperacusis	-	-	-	1-2	-	-
Labyrinthitis	-	-	-	-	-	1
Parosmia	-	-	-	≤2	-	-
Scleritis	-	-	-	-	≤1	≤1
Tinnitus	-	-	-	-	≤1	1
Visual disturbance	-	-	-	≤2	>1	1-3
Other						
Accidental injury/ trauma	-	≤3	-	-	≤1	1
Adenopathy	-	-	-	-	-	-
Allergic reactions	-	-	-	-	4	>1
Anaphylaxis	-	-	-	✔	-	-
Cystitis	-	-	-	-	≤1	≤1
Fever/hyperpyrexia	✔	-	-	≥1	≤1	1
Flu syndrome	-	✔	1	-	2	3
Gynecomastia (males)	-	≤3	-	-	-	-
Infection	-	-	-	-	1	≤1
Menstrual irregularities	-	≤3	-	3-4	≤1	1
Oliguria	-	-	-	-	-	-
Pain (nonspecific)	-	4-5	-	-	-	-
Sweating/ clamminess	-	-	-	-	≤1	≤1
Urinary frequency/ incontinence	-	-	-	-	≤1	≤1
Urinary hesitancy	-	-	-	-	-	-
Urinary tract infection	-	≤3	-	-	2	>1
Vaginitis	-	-	-	-	≤1	≤1
Viral infection	-	3	-	-	-	-

-Event not reported or incidence <1%
✔ Percent not specified
ECG=electrocardiogram, ER=extended release, IR=immediate release, SGPT=serum glutamic pyruvic transaminase (alanine aminotransferase)

Table 7. Black Box Warning for Chloral Hydrate[14]

WARNING
Chloral hydrate is genotoxic and may be carcinogenic in mice. Do not use chloral hydrate when less potentially dangerous agents would be effective.

Drug Abuse and Dependence

Chloral hydrate, eszopiclone, zaleplon and zolpidem are categorized as schedule C-IV by the Drug Enforcement Agency (DEA) because of their abuse potential. The risk of abuse and dependence increases with the dose and duration of treatment and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol or drug abuse or history of psychiatric disorders. There are limited studies that have evaluated the long-term safety and efficacy of these agents. There was no

evidence of tolerance to eszopiclone with up to 12 months of nightly use, and no significant withdrawal symptoms were observed after discontinuation.[2] The longest placebo-controlled studies with zaleplon were 4 weeks in duration.[2] In these studies, zaleplon use did not appear to result in rebound insomnia, withdrawal symptoms or tolerance. After 4 weeks of nightly use, withdrawal symptoms and rebound insomnia have been reported upon discontinuation of zolpidem; however, the potential for dependence, tolerance or rebound insomnia appears minimal when zolpidem is used at the recommended dosages.[2] Tolerance, rebound insomnia or withdrawal effects have not been observed with ramelteon.[5]

VII. Dosing and Administration

The usual dosing regimens for the non-benzodiazepine, non-barbiturate sedative hypnotics are summarized in Table 8.

Table 8. Usual Dosing for the Non-Benzodiazepine, Non-Barbiturate Sedative Hypnotics [6-8,10-15]

Drug	DEA Schedule	Usual Adult Dose	Usual Pediatric Dose	Availability
Chloral hydrate	IV	Alcohol Withdrawal Syndrome: 500 mg-1 g orally or rectally every six hours as needed; generally single doses or daily dosage should not exceed 2 g Hypnotic Dose: 500 mg-1 g orally or rectally 15-30 minutes before bedtime or, when used as a preoperative medication, 30 minutes before surgery Sedative Dose: 250 mg three times a day after meals; generally single doses or daily dosage should not exceed 2 g	Hypnotic Dose: 50 mg/kg or 1.5 g/m^2 orally or rectally; maximum single dose: 1 g Sedative Dose: 8 mg/kg or 250 mg/m^2 three times a day; maximum dose: 500 mg three times a day Premedication for Electroencephalographic Evaluation: 20-25 mg/kg	Capsule: 500 mg Suppository: 324 mg 500 mg Syrup: 500 mg/5 mL
Eszopiclone	IV	Insomnia: Nonelderly adults: initial, 2 mg immediately before bedtime; dose may be increased to 3 mg Elderly adults: initial, 1 mg immediately before bedtime if main complaint is difficulty falling asleep; 2 mg immediately before bedtime if main complaint is difficulty staying asleep Severe hepatic impairment: initial, 1 mg	Safety and efficacy in children <18 years have not been established.	Tablet: 1 mg 2 mg 3 mg
Ramelteon	Not a controlled substance	Insomnia: 8 mg taken within 30 minutes before going to bed	Safety and efficacy in children have not been established.	Tablet: 8 mg
Zaleplon	IV	Insomnia: Nonelderly adults: 10 mg at bedtime; maximum dose: 20 mg Elderly patients and debilitated patients: 5 mg at bedtime; maximum dose: 10 mg	Safety and efficacy in children have not been established.	Capsule: 5 mg 10 mg

Drug	DEA Schedule	Usual Adult Dose	Usual Pediatric Dose	Availability
		Patients with mild-to-moderate hepatic impairment: 5 mg at bedtime		
Zolpidem	IV	Insomnia: Nonelderly adults: 10 mg IR tablet or 12.5 mg ER tablet immediately before bedtime Elderly, debilitated patients or patients with hepatic insufficiency: 5 mg IR tablet or 6.25 mg ER tablet immediately before bedtime	Safety and efficacy in children <18 years old have not been established.	Tablet, immediate-release (IR): 5 mg 10 mg Tablet, extended-release (ER): 6.25 mg 12.5 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the non-benzodiazepine, non-barbiturate sedative hypnotics are summarized in Table 9.

Table 9. Comparative Clinical Trials Using the Non-Benzodiazepine, Non-Barbiturate Sedative Hypnotics

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Insomnia				
Piccione et al[17] Chloral hydrate 250 mg vs chloral hydrate 500 mg vs triazolam 0.25 mg vs triazolam 0.50 mg vs placebo Participants received each of the 5 treatments on 5 consecutive nights.	DB, XO Elderly (>60 years) patients with insomnia	N=27 5 days	Primary: Efficacy (questionnaire with subjective estimates of sleep latency, total sleep time [TST], number of awakenings, overall quality of sleep), side effects Secondary: Not reported	Primary: The patients' global evaluation of effectiveness indicated that triazolam 0.25 mg and 0.50 mg improved sleep more than placebo (both $P<0.05$), while chloral hydrate 250 mg and 500 mg were not better than placebo (P values not reported). Triazolam 0.50 mg but not 0.25 mg was felt to be significantly better than chloral hydrate 250 mg ($P<0.01$) and 500 mg ($P<0.05$) in the global evaluation of effectiveness. There was no significant difference in sleep latency, TST and number of awakenings between placebo and either dose of chloral hydrate (P values not reported). Triazolam 0.25 mg significantly decreased sleep latency and increased TST compared to placebo (both $P<0.05$). Triazolam 0.50 mg significantly decreased the number of awakenings compared to placebo ($P<0.01$). Patients estimated their TST to be longer following the use of triazolam 0.25 mg as compared to chloral hydrate 250 mg or 500 mg (both $P<0.05$). There were no significant differences in reported side effects between the active treatments and placebo. Secondary: Not reported
Zammit et al[18] Eszopiclone 2 mg or 3 mg	DB, MC, PC, RCT	N=308 6 weeks	Primary: Efficacy (polysomnography	Primary: Eszopiclone 2 mg and 3 mg had significantly less time to sleep onset ($P\leq0.001$ and $P\leq0.0001$, respectively), more TST ($P\leq0.01$ and $P\leq0.0001$),

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	Adults aged 21-64 years with chronic primary insomnia		[PSG] and patient reports), next day residual effects (Digit-Symbol Substitution Test [DSST]), tolerance, rebound insomnia, safety Secondary: Not reported	better sleep efficiency ($P \leq 0.001$ and $P \leq 0.0001$), and enhanced quality and depth of sleep (both $P<0.05$) across the double-blind period compared with placebo. Eszopiclone 3 mg ($P \leq 0.01$) but not 2 mg significantly improved sleep maintenance compared to placebo. Median DSST scores showed no decrement in psychomotor performance relative to baseline and did not differ from placebo in either eszopiclone group. There was no evidence of tolerance or rebound insomnia after therapy discontinuation. Treatment was well tolerated; unpleasant taste was the most common adverse event reported with eszopiclone. Secondary: Not reported
Scharf et al[19] Eszopiclone 1 mg or 2 mg vs placebo	DB, MC, PC, RCT Community-dwelling elderly patients (mean age 72.3 years) with primary insomnia	N=231 2 weeks	Primary: Patient-reported efficacy (sleep latency, TST) Secondary: Wake time after sleep onset (WASO), number of awakenings, number and length of naps, quality of sleep, depth of sleep, ratings of daytime alertness, sense of physical well-	Primary: Patients treated with eszopiclone 1mg and 2 mg had a significantly shorter sleep latency compared with placebo ($P<0.05$ and $P=0.0034$, respectively). The eszopiclone 2-mg group ($P=0.0003$) but not the 1-mg group ($P>0.1$) had significantly longer TST compared to placebo. Secondary: Compared to placebo, patients receiving eszopiclone 2 mg had significantly less WASO but similar number of awakenings per night ($P>0.1$). Patients receiving eszopiclone 2 mg had significantly fewer ($P=0.028$) and shorter in duration ($P=0.011$) daytime naps, higher ratings of sleep quality ($P=0.0006$) and depth ($P=0.0015$), better daytime alertness ($P=0.022$) and sense of physical well-being ($P=0.047$) compared with placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			being, morning sleepiness, ability to function, quality of life (Quality of Life Enjoyment and Satisfaction Questionnaire [Q-LES-Q]), safety	The differences between eszopiclone 2 mg and placebo were marginally significant for morning sleepiness (P=0.055) and ability to function (P=0.058). Duration of nap was significantly shorter in the eszopiclone 1-mg group compared to placebo (P<0.05); however, there were no other significant differences in any other secondary efficacy endpoints. Compared to placebo, the eszopiclone 2-mg group had significantly higher quality of life scores on 5 of the 16 Q-LES-Q domains (physical health, mood, household activities, leisure time activities and medications; P<0.05). The differences between eszopiclone 2 mg and placebo were marginally significant for the Q-LES-Q global score (P=0.064). There were no significant differences between eszopiclone 1 mg and placebo for any of the Q-LES-Q dimensions. Eszopiclone was well tolerated with unpleasant taste reported as the most frequent treatment-related adverse event.
Krystal et al[20] Eszopiclone 3 mg (N=593) vs placebo (N=195)	DB, MC, PC, RCT Adults with chronic insomnia	N=788 6 months	Primary: Sleep latency, WASO, number of awakenings, TST, quality of sleep, next-day ratings of ability to function, daytime alertness, sense of physical well-being, safety Secondary: Not reported	Primary: At the first week and each month for the study duration, eszopiclone produced significant and sustained improvements in sleep latency, WASO, number of awakenings, number of nights awakened per week, TST, and quality of sleep compared to placebo (all $P \leq 0.003$). Monthly ratings of next-day function, alertness, and sense of physical well-being were also significantly better with the use of eszopiclone than with placebo (all $P \leq 0.002$). There was no evidence of tolerance and the most common adverse events were unpleasant taste and headache. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Walsh et al[21] Eszopiclone 3 mg (N=550) vs placebo (N=280)	DB, MC, PC, RCT Adults aged 21-64 years with primary insomnia	N=830 26 weeks	Primary: Patient-reported sleep measures (sleep latency, WASO, TST, number of awakenings, sleep quality, daytime alertness, ability to concentrate, physical well-being, and ability to function), Insomnia Severity Index, Fatigue Severity Scale, Epworth Sleepiness Scale, Medical Outcomes Study Short-Form Health Survey (SF-36), Work Limitations Questionnaire, safety (assessments performed at baseline, treatment Months 1-6, and 2 weeks after discontinuation of treatment) Secondary: Not reported	Primary: Patient-reported sleep and daytime function improved more with eszopiclone than with placebo at all months (P<0.001). Eszopiclone reduced Insomnia Severity Index scores to below clinically meaningful levels for 50% of patients (vs 19% with placebo; P<0.05) at 6 months. Lower mean scores on the Fatigue Severity Scale and the Epworth Sleepiness Scale were observed in the eszopiclone group relative to placebo for each month and the Month 1-6 average (P<0.05). SF-36 domains of Physical Functioning, Vitality, and Social Functioning were improved with eszopiclone vs placebo for the Month 1-6 average (P<0.05). Similarly, improvements were observed for all domains of the Work Limitations Questionnaire with eszopiclone vs placebo for the Month 1-6 average (P<0.05). There was no evidence of rebound insomnia after discontinuation of eszopiclone as sleep latency, WASO and TST remained significantly improved from baseline (all P<0.001). There were no between-treatment differences observed during the discontinuation period except for a significantly greater sleep latency on the first night after discontinuation with eszopiclone vs placebo (45 vs 30 minutes; P=0.015). No significant group differences were observed in mean Benzodiazepine Withdrawal Symptom Questionnaire scores (3.0 with eszopiclone and 2.3 with placebo, P=0.12), or overall adverse event rates (15.2% for eszopiclone and 11.1% for placebo, P value not reported). Unpleasant taste (19.7% vs 1.1%; P<0.001), somnolence (8.8% vs 3.2%; P=0.0029), and myalgia (6.0% vs 2.9; P=0.047) were reported in significantly more patients receiving eszopiclone than placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Rosenberg et al[22] Eszopiclone 1 mg, 2 mg, 3 mg or 3.5 mg vs placebo	DB, PC, RCT Healthy adult volunteers with transient insomnia	N=436 1 night	Primary: Efficacy and next-morning effects evaluated by PSG, DSST and self report Secondary: Not reported	Primary: Patients treated with eszopiclone had significantly less PSG latency to persistent sleep (all doses except 1 mg; $P \leq 0.0001$), WASO (all doses; $P \leq 0.05$) and number of awakenings (3 and 3.5 mg doses; $P < 0.005$), and greater sleep efficiency (all doses; $P \leq 0.02$) compared with placebo. Self-reported efficacy results were similar to PSG. Self-reported morning sleepiness scores were significantly better for eszopiclone 3 and 3.5 mg compared with placebo ($P < 0.05$). Treatment was well tolerated by patients, and the most common treatment-related adverse event was unpleasant taste. Secondary: Not reported
Johnson et al[23] Ramelteon 16mg, 80 mg or 160 mg vs triazolam 0.25 mg, 0.5 mg or 0.75 mg vs placebo	DB, XO Adults with history of sedative abuse	N=14 18 days	Primary: Subject-rated measures (drug liking, street value, pharmacological classification), observer-rated measures (sedation, impairment), motor and cognitive performance (balance task, DSST, word recall) Secondary:	Primary: Compared with placebo, all doses of ramelteon showed no significant effect on any of the subjective effect measures, including those related to potential for abuse (all $P > 0.05$). In the pharmacological classification, 79% of subjects identified the highest dose of ramelteon as placebo. Compared with placebo, ramelteon had no effect at any dose on any observer-rated or motor and cognitive performance measure (all $P > 0.05$). Triazolam showed dose-related effects on subject-rated, observer-rated, and motor and cognitive performance measures. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Not reported	
Roth et al [24] Ramelteon 16 mg vs ramelteon 64 mg vs placebo Doses were given 30 minutes before bedtime.	DB, PC, MC, RCT Healthy adult volunteers with transient insomnia (aged 35-60 years with total sleep duration of 6.5-8.5 hours, a usual sleep latency of 30 minutes or less, a habitual bedtime between 8:30 PM and midnight)	N =375 1 night	Primary: Mean latency to persistent sleep (LPS) as measured by PSG Secondary: TST, WASO, percentage of sleep time in each sleep stage, number of awakenings, residual effects assessed by DSST and postsleep questionnaire, safety	Primary: Participants who had received either ramelteon dosage had significantly shorter LPS relative to placebo (both $P<0.001$). Secondary: Participants who had received ramelteon 16 mg or 64 mg had significantly longer TST compared with placebo ($P=0.007$ and $P=0.033$, respectively). There were no significant differences between the ramelteon groups and placebo with regards to WASO, percentage of sleep time in each sleep stage, and number of awakenings. No significant differences in DSST scores were reported among the groups, but ramelteon 64 mg was associated with statistically significant declines in subjective levels of alertness ($P=0.020$) and ability to concentrate ($P=0.043$) compared to placebo. No serious adverse events were reported.
Roth et al[25] Ramelteon 4 mg vs ramelteon 8 mg vs placebo Doses were given at night.	DB, PC, RCT Patients aged 64-93 years with chronic primary insomnia	N=829 5 weeks	Primary: Sleep latency at week 1 Secondary: TST at weeks 1, 3 and 5; reductions in sleep latency at weeks 3 and 5; sleep diaries; rebound insomnia and withdrawal effects during the 7-day placebo run out	Primary: Significant reductions in sleep latency at week 1 were reported with both ramelteon 4 mg (70.2 vs 78.5 minutes, $P=0.008$) and 8 mg (70.2 vs 78.5 minutes, $P=0.008$) compared with placebo. Secondary: Patients continued to report reduced sleep latency at week 3 with ramelteon 8 mg ($P=0.003$) and at week 5 with ramelteon 4 and 8 mg ($P=0.028$ and $P<0.001$, respectively) compared to placebo. Patient-reported TST at weeks 1 and 3 was significantly longer compared to placebo for ramelteon 4 mg (324.6 vs 313.9 minutes, $P=0.004$ and 336.0 vs 324.3 minutes, $P=0.007$, respectively). TST for ramelteon 4 mg at 5 weeks and for ramelteon 8 mg at weeks 1, 3 and 5 were longer than placebo but did

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				not reach statistical significance (*P* values >0.05). Analyses of other sleep parameters obtained via sleep diaries (eg, number of awakenings, ease of falling back asleep after an awakening and sleep quality) yielded no statistically significant differences among treatment groups at weeks 1, 3 and 5. There was no evidence of significant rebound insomnia or withdrawal effects following treatment discontinuation. Incidence of adverse events was 51.5%, 54.8% and 58.0% of patients in the placebo, 4 mg and 8 mg ramelteon groups, respectively.
Erman et al[26] Ramelteon 4 mg, 8 mg, 16 mg or 32 mg vs placebo Patients received all 5 treatments, with a 5- to 12-day washout between treatments. Medication was administered 30 minutes before bedtime.	DB, MC, PC, RCT, 5-period XO Men and non-pregnant, non-lactating women between 18-64 years of age with chronic insomnia	N =107 2 nights per treatment	Primary: Mean LPS Secondary: TST, WASO, percentage of sleep time in each sleep stage, subjective sleep quality, next-day performance and alertness, safety	Primary: All tested doses of ramelteon resulted in statistically significant reductions in LPS compared to placebo (*P*<0.001). Secondary: All tested doses of ramelteon resulted in statistically significant increases in TST compared with placebo (*P*=0.001). No significant differences in WASO (*P*=0.470), percentage of time spent in the different sleep stages and subjective sleep quality (*P*=0.525) were reported between the ramelteon groups and placebo. There were no differences between placebo and any ramelteon dose group on next-day performance and alertness (*P* values not reported). The safety of ramelteon at each dose was similar to that of placebo and the most commonly reported adverse events were headache, somnolence, and sore throat.
Danjou et al[27] Zaleplon 10 mg	DB, XO Healthy	N=36 13 days	Primary: Subjective and objective	Primary: No residual effects were demonstrated after zaleplon 10 mg, when administered as little as 2 hours before waking, on either subjective or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs zolpidem 10 mg vs placebo	volunteers, mean age 29.5 years		measurements of residual effects when study drug was given 5, 4, 3, or 2 hours before morning awakening, tests included DSST, Critical Flicker Fusion (CFF) threshold, Choice Reaction Time (CRT), Memory Test, Sternberg Memory Scanning Task, Leeds Analogue Rating Scales (LARS), Leeds Sleep Evaluation Questionnaire (LSEQ), adverse events Secondary: Not reported	objective assessments. Zolpidem 10 mg showed significant residual effects on DSST and memory after administration up to 5 hours before waking and CRT, CFF threshold and Sternberg Memory Scanning Task after administration up to 4 hours before waking. Residual effects of zolpidem were apparent in all objective and subjective measurements when the drug was administered later in the night. There were no serious adverse experiences during the study; all adverse events were mild-to-moderate. Overall, the number of subjects who reported any adverse experience after administration of study drug was similar for zaleplon and placebo (11% and 33% regardless of the time of drug administration) but was significantly higher following zolpidem (56% to 72%) when zolpidem was administered 2, 3, 4, and 5 hours before awakening (*P* values not reported). Secondary: Not reported
Verster et al[28] Zaleplon 10 mg vs zaleplon 20 mg vs zolpidem 10 mg	DB, XO Healthy volunteers with mean age 24.0 years	N=30 Single dose with at least a 5-day washout period	Primary: Driving ability (standard deviation of the lateral position [SDLP], standard deviation of speed [SDS], memory, psychomotor performance) (subjects given study medication 5 hours	Primary: Zaleplon 10 and 20 mg did not significantly impair driving ability 4 hours after middle-of-the-night administration (significant difference defined as $P<0.0125$). Relative to placebo, after zolpidem 10 mg, SDLP (amount of weaving of the car) was significantly elevated but the magnitude of the difference was small and not likely to be of clinical importance (difference was 2.87 cm; $P<0.005$). SDS (speed variability) was not significantly different for zolpidem 10 mg than placebo ($P=0.256$). Zolpidem 20 mg significantly increased SDLP and speed variability (both $P<0.001$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs zolpidem 20 mg vs placebo This was a 2-part study with the first part evaluating the effect of ethanol and the second part evaluating the effects of zaleplon and zolpidem. Only the second part of the study was reported in this review.			after going to bed and awakened 3 hours after dose, driving test performed 4 hours after awakened, memory and psychomotor tests performed 6 hours after awakened) Secondary: Not reported	Memory and psychomotor test performances were unaffected after both doses of zaleplon and zolpidem 10 mg. Zolpidem 20 mg significantly impaired performance on psychomotor and memory tests. (Note: the recommended dose for zolpidem is 10 mg immediately before bedtime.) Secondary: Not reported
Dunbar et al[29] Zaleplon 5 mg to 20 mg vs zolpidem 5 mg to 10 mg The complete meta-analysis included 24 studies in 3,909 patients of which 17 studies compared zaleplon, zolpidem or zopiclone* to a benzodiazepine, 1 study compared zolpidem to zopiclone* and 6 studies	MA, DB, PG, RCT, XO Patients aged 16-85 years with insomnia	6 trials N=1,539 Duration varied (2 nights to 4 weeks)	Primary: Sleep onset latency, TST, quality of sleep, adverse events, rebound insomnia Secondary: Not reported	Primary: Of the 2 studies that directly compared sleep onset latency, 1 study reported a significantly shorter sleep latency with zaleplon (P<0.001), whereas the other study reported results in favor of zolpidem (P=0.03). Of the 2 studies that directly compared TST, 1 study reported that sleep duration was significantly less in the zaleplon group (290.7 minutes vs 308.6 minutes for zolpidem, P=0.05) but another study found no difference (8 hours for zaleplon vs 8.3 hours on zolpidem, P value not reported). Patients on zaleplon were less likely to experience an improvement in sleep quality than those on zolpidem (OR: 0.66; 95% CI: 0.51 to 0.87). There was no statistically significant difference in the frequency of treatment-emergent adverse events (OR: 0.86; 95% CI: 0.62 to 1.20).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
compared zaleplon to zolpidem. Only the results of the studies comparing zaleplon to zolpidem are included in this review.				One study reported that patients taking zaleplon were less likely to suffer withdrawal symptoms on the first night of the placebo run-out phase than those on zolpidem (1.5% and 7.1% respectively, *P*=0.01). Combined results from 2 trials noted that patients receiving zaleplon were less likely to experience rebound insomnia compared with those on zolpidem (sleep latency OR: 0.27; 95% CI: 0.17 to 0.44, sleep duration OR: 0.25; 95% CI 0.15 to 0.41, and number of awakenings OR: 0.34; 95% CI 0.18 to 0.61). In a crossover study, 62.3% of patients favored zolpidem compared with 37.7% of patients who favored zaleplon (*P*=0.08). Secondary: Not reported
Elie et al[30] Zaleplon 5, 10 or 20 mg or zolpidem 10 mg vs placebo After 28 days, all treatments were followed by placebo for 3 nights.	DB, MC, PC, RCT Adults with primary insomnia or insomnia associated with mild nonpsychotic psychiatric disorders	N=615 4 weeks	Primary: Patient's assessment of sleep latency Secondary: Patient's assessment of sleep duration, sleep quality, number of awakenings, rebound insomnia, withdrawal effects, safety	Primary: Median sleep latency was significantly lower with zaleplon 10 mg and 20 mg than with placebo during all 4 weeks of treatment, and with zaleplon 5 mg and zolpidem 10 mg for the first 3 weeks. Secondary: Zaleplon 20 mg significantly ($P \leq 0.05$) increased sleep duration compared with placebo in all but week 3 of the study, while zolpidem 10 mg significantly ($P \leq 0.05$) increased sleep duration at all time points. Mean scores for sleep quality were significantly ($P \leq 0.05$) better than with placebo during week 1 with zaleplon 10 mg and 20 mg, and for all weeks with zolpidem 10 mg. No significant differences were observed in number of awakenings between the placebo and active treatment groups (*P* values not reported). The number of patients treated with zaleplon showing rebound insomnia

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				was not significantly different from placebo on the first night after discontinuation of 4 weeks of treatment. Significant differences in sleep latency ($P \leq 0.05$) and number of awakenings ($P \leq 0.01$) were noted in patients treated with zolpidem 10 mg. On the second night after discontinuation of treatment, there were significantly more patients ($P \leq 0.05$) showing rebound insomnia for the number of awakenings with zaleplon 10 mg and 20 mg than with placebo, and on the third night there were significantly fewer patients ($P \leq 0.05$) showing rebound for the number of awakenings with zaleplon 20 mg. There was no evidence of withdrawal symptoms after discontinuation of 4 weeks of zaleplon treatment. Significantly more patients who had received zolpidem than placebo reported withdrawal effects on the first night after treatment was discontinued; however, there was no statistically significant difference on the second or third night between the 2 groups. The frequency of adverse events in the active treatment groups did not differ significantly from that in the placebo group. The study did not report any direct comparisons between the zaleplon.
Roth et al[31] Zolpidem 5, 7.5, 10, 15, 20 mg vs placebo Statistical analyses were primarily performed between zolpidem 7.5 and 10 mg and	DB, PC, PG, RCT Healthy adult volunteers with transient insomnia	N=462 Single dose	Primary: Sleep latency, sleep duration, sleep efficiency (total sleep time divided by time in bed) number of awakenings (sleep maintenance), effect on sleep stages, next day psychomotor performance and alertness (DSST,	Primary: Compared to placebo, zolpidem 7.5 and 10 mg significantly decreased sleep latency, increased sleep duration and efficiency, and reduced the number of awakenings (all $P<0.05$). Subjective quality of sleep was also rated significantly better with both doses of zolpidem compared to placebo (both $P<0.001$). Increasing the dose above 10 mg did not result in a corresponding increase in hypnotic efficacy. Treatment with zolpidem had no effect on stage 1, stage 2 and stages 3-4 sleep. Significantly less rapid eye movement (REM) sleep was reported in the zolpidem groups compared to the placebo group (both $P<0.001$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo.			Symbol Copying Tests, Visual Analog Scales on the Morning Questionnaire) Secondary: Not reported	Zolpidem 7.5 or 10 mg had no significant effect on next day psychomotor performance and alertness. No statistically significant differences in the overall side effects were found between zolpidem doses of 7.5 mg (4.9%) or 10 mg (6.7%) and placebo (7.8%). Higher doses of zolpidem were associated with more side effects (17.6% with 15 mg [*P*=0.069 vs placebo] and 31.4% with 20 mg [*P*<0.001 vs placebo]). Secondary: Not reported
Scharf et al[32] Zolpidem 10 or 15 mg vs placebo Patients were randomized to receive either zolpidem or placebo for 35 nights, followed by placebo for 3 additional nights.	DB, MC, PC, PG, RCT Adults with chronic insomnia	N=75 5 weeks	Primary: LPS, sleep efficiency, sleep maintenance, sleep quality, effects on sleep stages, residual drug effects, safety Secondary: Not reported	Primary: Zolpidem had a significant (*P*<0.05) effect on LPS and sleep efficiency from weeks 2 through 5 in the 10-mg group and at weeks 2 through 6 in the 15-mg group. Polysomnographic measures of sleep maintenance were not significantly different among the 3 treatment groups (*P*>0.05). Patients receiving zolpidem 15 mg reported significantly better quality of sleep than those receiving the 10 mg dose at week 2 and placebo at week 5. Stages 1, 2, and 3-4 sleep were not significantly affected by either the 10- or 15-mg doses of zolpidem compared with placebo. However, there were significant (*P*<0.05) decreases in REM sleep at weeks 3 and 4 with zolpidem 15 mg compared with placebo. There was no evidence of residual effect with zolpidem 10 or 15 mg. There was no evidence of tolerance at either dose. The only significant treatment difference was in the percent of time in Stage 3-4 sleep (*P*<0.05 for both zolpidem doses compared to placebo).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There were no significant treatment differences between the 10-mg zolpidem group and placebo in LPS, sleep efficiency, wake time during sleep or sleep quality during the posttreatment period when zolpidem was discontinued. The 15-mg zolpidem group did not differ significantly from the placebo group on LPS or sleep efficiency on the first night posttreatment, but did result in a significantly greater wake time during sleep and poorer quality of sleep (P<0.05 compared to placebo) during the first night posttreatment. Comparison of the subsequent 2 nights posttreatment showed no significant differences between zolpidem 15 mg and placebo on any of these variables. Overall, the incidence of treatment emergent adverse events in the zolpidem groups was similar to those in the placebo group. While none of the adverse events were severe, 2 patients in the 15-mg zolpidem group withdrew from the study: 1 patient experienced drowsiness, dizziness, and nausea; and 1 patient experienced visual disturbance and oversedation. The 15-mg zolpidem dosage provided no clinical advantage over the 10 mg zolpidem dosage. Secondary: Not reported
Hindmarch et al[33] Zolpidem, modified release (MR) 6.25 mg vs zolpidem MR 12.5 mg vs	DB, DD, RCT, XO Healthy volunteers at least 65 years of age	N=24 Single dose, treatment visits lasted 2 days and were separated by 28-42 days washout	Primary: Psychometric tests performed 8 hours after study medication (CFF, CRT, word recall, CTT, DSST), subjective evaluation of sleep (LSEQ), safety, pharmacokinetics (zolpidem MR only)	Primary: There were no significant differences in psychometric tests between either dose of zolpidem MR and placebo (P<0.05). Psychometric performance was significantly impaired (P<0.05) with flurazepam compared to placebo for all tests with the exception of the DSST (P=0.0526). Ease of falling asleep and sleep quality were significantly improved with both doses of zolpidem MR and with flurazepam (all P<0.05). Neither zolpidem MR nor flurazepam modified perception of well-being on awakening (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
flurazepam 30 mg vs placebo			Secondary: Not reported	The frequency of adverse events was similar in all four treatment conditions. None of the adverse events was serious or led to withdrawal from the study. The plasma concentration ratio was 1.96 between the two doses of zolpidem MR, which is consistent with dose linearity. Secondary: Not reported
Erman et al[34] Eszopiclone 1 mg, 2 mg, 2.5 mg, or 3 mg for two nights vs zolpidem 10 mg for two nights vs placebo for two nights	R, MC, XO Patients with primary insomnia aged 21-64 years	N=65 Single dose, treatment visits lasted 2 days and were separated by 3-7 days washout	Primary: Latency to persistent sleep Secondary: Sleep efficiency, wake time after sleep onset, wake time during sleep, number of awakenings, adverse effects	Primary: Compared to placebo, all active groups exhibited a statistically significant improvement in the primary endpoint (P<0.05). Secondary: Compared to placebo, all active groups exhibited a statistically significant improvement in sleep efficiency (P<0.05). Compared to placebo, the eszopiclone 3 mg group exhibited a statistically significant improvement in wake time after sleep onset, wake time during sleep, and the number of awakenings (P<0.05). However a significant difference from placebo in these secondary endpoints was not seen in either zolpidem 10 mg, or the lower dose eszopiclone groups (P>0.05). The incidence of CNS adverse effects was 23.4% for zolpidem 10 mg, 6.2%-12.5% for eszopiclone doses, and 7.9% for placebo.
Smith et al[35] Benzodiazepines (flurazepam, quazepam, triazolam, lorazepam, midazolam): 6 trials or	MA Patients with primary insomnia for 1 month or longer	21 trials N=470 Duration varied (<1 week to 10 weeks)	Primary: Sleep latency, TST, number of awakenings, WASO, and sleep quality before and after treatment	Primary: Sleep latency was reduced by 30% with pharmacological treatment compared with 43% with behavioral interventions. Pharmacotherapy increased TST by 12% and behavior therapy by 6%. Both pharmacotherapy and behavior therapy reduced number of awakenings per night by 1.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
benzodiazepine receptor agonists (zolpidem, zopiclone*): 2 trials vs behavioral treatment: 14 trials vs placebo One trial directly compared pharmacotherapy with a benzodiazepine (temazepam) and behavioral therapy.			Secondary: Not reported	WASO was reduced by 46% with pharmacotherapy and by 56% with behavior therapy. Pharmacotherapy improved sleep quality by 20% and behavior therapy by 28%. Overall, there were no differences in TST, number of awakenings, WASO, and sleep quality between benzodiazepine receptor agonists and behavioral therapy. The behavioral therapy group had a greater reduction in latency to sleep onset than the group that took the benzodiazepine receptor agonists (95% CI: 0.17-1.04) Secondary: Not reported
Nowell et al[36] Benzodiazepines (estazolam: 6 trials, flurazepam: 10 trials, lorazepam: 1 trial, quazepam: 3 trials, temazepam: 3 trials, triazolam: 4 trials) or zolpidem: (5 trials) vs placebo	MA of 22 trials (from 1978-1996); DB, PC, RCT, XO Adults <65 years with chronic insomnia	22 trials N=1,894 Median duration of 7 days, range 4 to 35 days	Primary: Sleep latency, TST, number of awakenings, sleep quality Secondary: Not reported	Primary: Zolpidem and benzodiazepines were significantly more effective than placebo with regards to sleep latency, TST, number of awakenings and sleep quality ($P<0.001$). Secondary: Not reported Note: This meta-analysis did not compare the efficacy of zolpidem to benzodiazepines.
Buscemi et al[37] Benzodiazepines (52 trials including brotizolam*,	MA of 105 trials (up to July 2006); DB, PC, RCT	105 trials N varied, range 6 to 1,507	Primary: Sleep latency, WASO, sleep efficiency, sleep quality, TST, adverse	Primary: Sleep latency assessed by PSG was significantly decreased for benzodiazepines (WMD: -10.0 minutes; 95% CI: -16.6 to -3.4), nonbenzodiazepines (WMD: -12.8 minutes; 95% CI: -16.9 to -8.8) and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
estazolam, flunitrazepam*, flurazepam, loprazolam*, lorazepam, lormetazepam*, nitrazepam*, quazepam, temazepam and triazolam) or nonbenzodiazepines (48 trials including eszopiclone, gaboxadol*, indiplon*, zaleplon, zolpidem and zopiclone*) or antidepressants (8 trials including doxepin, pivagabine*, trazodone and trimipramine) vs placebo (105 trials) Some trials had multiple treatment arms.	Adults with chronic insomnia	Duration varied (1 night to 6 months)	events Secondary: Not reported	antidepressants (WMD: -7.0 minutes; 95% CI: -10.7 to -3.3). Sleep latency assessed by sleep diaries was also significantly improved for benzodiazepines (WMD: -19.6 minutes; 95% CI: -23.9 to -15.3), nonbenzodiazepines (WMD: -17.0 minutes; 95% CI: -20.0 to -14.0) and antidepressants (WMD: -12.2 minutes; 95% CI: -22.3 to -2.2). Meta-analyses for WASO, sleep efficiency, sleep quality and TST measured by PSG and sleep diary were statistically significant and favored benzodiazepines and nonbenzodiazepines vs placebo with the exception of PSG studies measuring WASO and TST, which were marginally nonsignificant. In contrast, PSG results significantly favored antidepressants vs placebo, but sleep diary results were fewer and nonsignificantly favored antidepressants for WASO and nonsignificantly favored placebo for TST. (*P* values were not reported.) Indirect comparisons between benzodiazepines and nonbenzodiazepines resulted in no significant difference in sleep latency; however, benzodiazepines were associated with more adverse events (*P* value not reported). Indirect comparisons between benzodiazepines and antidepressants resulted in no significant difference in sleep latency or adverse events (*P* values not reported). Indirect comparisons between nonbenzodiazepines and antidepressants resulted in a significantly greater sleep latency assessed by PSG but not by sleep diary for nonbenzodiazepines. There was no significant difference in adverse events. (*P* values were not reported.) All drug groups had a statistically significant higher risk of harm (more adverse events) compared to placebo, although the most commonly reported adverse events were minor. Risk differences were 0.15, 0.07 and 0.09 for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the benzodiazepines, nonbenzodiazepines and antidepressants, respectively, compared to placebo. The adverse events most commonly reported in these studies were headache, drowsiness, dizziness and nausea. Secondary: Not reported

*Not available in the United States
Drug regimen abbreviations: AM=morning, BID=twice daily, HS=bedtime, MAOI=monoamine oxidase inhibitor, PM=evening, QD=once daily, QID=four times daily, SSRI=selective serotonin-reuptake inhibitor, TID=three times daily, XR=extended-release
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NNT=numbers needed to treat, NS=not significant, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover, WMD=weighted mean difference
Miscellaneous abbreviations: CFF=Critical Flicker Fusion, CNS=central nervous system, CRT=Choice Reaction Time, CTT=Continuous Tracking Test, DSST=Digit-Symbol Substitution Test, LARS=Leeds Analogue Rating Scales, LSEQ=Leeds Sleep Evaluation Questionnaire, LPS=latency to persistent sleep, PSG=polysomnography, Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire, REM=rapid eye movement, TST=total sleep time, WASO=wake time after sleep onset

Tolerance

There are limited studies that have evaluated the long-term safety and efficacy of these agents. Chloral hydrate has been found to lose effectiveness for both inducing and maintaining sleep by the end of a 2-week period of drug administration.[14] There was no evidence of tolerance to eszopiclone with up to 12 months of nightly use, and no significant withdrawal symptoms were observed after discontinuation.[2] The longest placebo-controlled studies with zaleplon were 4 weeks in duration.[2] In these studies, zaleplon use did not appear to result in rebound insomnia, withdrawal symptoms or tolerance. After 4 weeks of nightly use, withdrawal symptoms and rebound insomnia have been reported upon discontinuation of zolpidem; however, the potential for dependence, tolerance or rebound insomnia appears minimal when zolpidem is administered at the recommended dosages.[2]

Tolerance, rebound insomnia or withdrawal effects have not been observed with ramelteon when administered nightly for up to 6 months.[5,13]

IX. Conclusions

The non-benzodiazepine, non-barbiturate sedative hypnotics are primarily used for the treatment of insomnia. Chloral hydrate, zaleplon, and zolpidem immediate-release tablets are FDA approved for the short-term treatment of insomnia, while eszopiclone, ramelteon and zolpidem extended-release tablets are labeled for insomnia (without a time restriction). Clinical studies have shown that eszopiclone, ramelteon and zolpidem extended-release tablets retained their efficacy out to 12 months, 6 months and 3 weeks, respectively. Currently, there are no guidelines that recommend one pharmacological agent as a first-line therapy choice in treatment of insomnia. Behavioral therapy has been shown to be effective and is recommended as an option for the management of chronic insomnia.[2,4,5] A review of 21 trials concluded that behavioral therapy was more effective than zolpidem and zopiclone in latency to sleep onset and equally effective in total sleep time, number of awakenings, wake time after sleep onset, and sleep quality.[35]

Direct comparison trials of the agents within this class are limited and there is insufficient evidence that demonstrates that any agent in the class is safer or more effective than another. Chloral hydrate, zolpidem, and zaleplon are available in at least one generic dosage form or strength.

Appendix I: Other Insurance Coverage

Managed Care Organization	Current Coverage of Lunesta	Notes
MassHealth (Massachusetts Medicaid)	PA required	zolpidem, zaleplon no PA required at <10 units/month
New Hampshire Medicaid	Non preferred	zolpidem preferred
New York Medicaid	Non preferred	zolpidem, chloral hydrate preferred
MVP Healthcare	Tier 3, PA required	Tier 1: zolpidem, zaleplon, chloral hydrate
Cigna Healthcare	Tier 3, non preferred	Tier 1: zolpidem, zaleplon, chloral hydrate
Blue Cross Blue Shield of Vermont	Tier 3, QL	Tier 1: generics

Appendix II: Current Drug List (PDL) Alternatives

Medication	Cost/unit*	Dosing Frequency	Cost/30 days*
Lunesta, 1mg, 2mg, 3mg (eszopiclone)	*$5.79†*	*1-3mg daily HS*	*$173.70†*
chloral hydrate, 500mg/5ml	$0.015	500 mg to 2 g daily HS	$0.45-$1.80
zaleplon 5mg, 10mg (compare to Sonata®)	$0.72 - $0.74§	5-20 mg daily HS	$21.60 - $44.40
zolpidem, 5mg, 10mg (compare to Ambien®)	$0.25	5-10 mg daily HS	$7.50

* MAC as of 10/07/08
† AWP as of 10/07/08
§ FUL as of 11/12/08
HS=at bedtime

Appendix III: Most Recent Utilization Within this Drug Class for OVHA: January 1, 2008 to June 30, 2008

Medication	Unique Members	# of Rx's	% Marketshare	Plan Cost $	Avg $/Rx
Zolpidem	1,670	4,465	51.60	$47,820	$10.71
Lunesta	967	2,868	33.10	$375,481.43	$130.92
Ambien CR	207	730	8.43	$84,882.54	$116.28
Rozerem	108	339	3.92	$27,641.05	$81.54
Sonata	24	100	1.15	$8,030.74	$80.31
Ambien	22	87	1.00	$13,819	$158.84
Chloral hydrate	20	61	0.70	$401.81	$6.59
Somnote	2	7	0.08	$639.24	$91.32
Zaleplon	2	2	0.02	$207.50	$103.75
Class Total:	NA	8,659	100%	$558,923.31	$64.55

X. Recommendations

In recognition of the role of the non-benzodiazepine, non-barbiturate hypnotic agents as treatment for insomnia; their track record of efficacy & safety; cost; and the comparable safety and efficacy of all agents in the class, the following is recommended: generic zolpidem, generic zaleplon and chloral hydrate suppositories and oral syrup will be available without a prior authorization. All other products are recommended for nonpreferred status.

The following approval criteria is recommended for Ambien®, Ambien CR® and Lunesta®:

- The patient has had a documented side effect, allergy or treatment failure to zolpidem.

The following approval criteria is recommended for Sonata®:

- The patient has had a documented intolerance to generic zaleplon.

The following approval criteria are recommended for Rozerem®:

- The patient has had a documented side effect, allergy, or treatment failure to zolpidem.

OR

- There is a question of substance abuse with the patient or family of the patient.

No changes are recommended to the current approval criteria for Somnote®:

- The patient has had a documented side effect, allergy, or treatment failure with two medications not requiring prior-authorization from the sedative hypnotic:benzodiazepine and/or sedative hypnotic:non-benzodiazepine, non-barbiturate classes.

The following agents have a quantity limit of 1 tablet/day: zolpidem, Ambien®, Ambien CR®, Lunesta®, and Rozerem®. Zaleplon or Sonata® 5 mg have a quantity limit of 1 capsule/day and 10 mg has a quantity of 2 capsules/day.

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